REMARKS/ARGUMENTS

I. Status of the Claims

After entry of this amendment, claims 1-4, 6, 8, 10-17, 19-36, 38, 40, 42-49, 51, 52, 54, 55, 87-89, 91, 93, 95-102 and 104 are pending. Claims 5, 7, 9, 18, 37, 39, 41, 50, 52-53, 56-86, 90, 92, 94, 103, 105-106 are cancelled. Claims 22-30 are withdrawn. Claims 1-4, 6, 8, 10-17, 19-21, 31-36, 38, 40, 42-49, 51, 52, 54, 55, 87-89, 91, 93, 95-102 and 104 are currently presented. Claims 1, 6, 31, 38, 54, 55 and 91 are amended.

II. The Invention

It is the discovery of the present inventors that fucosyltransferases can be used *in vitro* to modify glycosylation patterns of glycopeptides. Accordingly the examined claims are drawn to *in vitro* methods for modifying glycosylation patterns of glycopeptides, including recombinantly produced glycopeptides using fucosyltransferases, especially fucosyltransferases that lack their membrane anchoring domain.

III. Support for the Amendments

See below.

IV. Responses to the Rejections

Over 35 U.S.C. §112, first paragraph, enablement

Claims 1-4, 6, 8, 10-17, 19-21, 31-36, 38, 40, 42-49, 51-53, 66-68, 70-77, 79-86 and 94 are rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. Claims 66-68, 70-77, 79-86 and 94 are cancelled. The Examiner states that

> the claims are not commensurate with the enablement provided by the disclosure with regard to the use of extremely large number of enzymes broadly encompassed by the claims and furthermore because of the characteristic nature of fucosyltransferases to altogether lose their specific activity to transfer fucose when the transmembrane domain is removed.
>
> December 29, 2005 Office Action, Page 4, lines 17-21

Applicants have amended the claims and therefore traverse this rejection.

Applicants have amended independent claims 1, 31, 54 and 55 in order to recite fucosylation performed only by FucT-VI, FucT-VII and combinations thereof. The efficacy of the claimed methods involving these two classes of fucosyltransferases have been experimentally demonstrated. In addition, the claimed methods are supported by the specification.

Prior to the filing of the application, enablement of the claimed methods involving FucT-VI, FucT-VII, and combinations thereof was demonstrated experimentally through a collaboration between the assignee, Neose, and Wyeth/Ayerst Pharmaceuticals. A March 2000, Feasibility Report from this project describes the success of the method. This Report is attached as Exhibit A. On page 2, Applicants summarize a study where glycopeptide fucosylation was demonstrated using FTVI (In Examples 72B and 72F on page 3 of Exhibit A), using FTVII (in Examples 72C and 72G) and using both FTVI and FTVII (Examples 72D and 72H). Examples 72A and 72E are controls and were not subjected to in vitro fucosylation. Table 3 on page 4 summarizes the results and is reprinted below:

Sample ID	% Disialylated Species (GI)		% Disialylated Species (Neose)	
	2SA_1Fuc	2SA_0Fuc	2SA_1Fuc	2SA_0Fuc
Ref Standard	40	60		
72A	14	86	19	81
72B	100	0	80	20
72C	100	0	78	22
72D	100	0	83	17
72E	26	74	30	70
72F	100	0	80	20
72G	100	0	75	25

72H	100	0	80	20

As shown above, fucosylation of over 75% was accomplished for each of the six Examples. The success of this method is further confirmed by a FACE gel of a reaction which involved FTVII. This FACE gel is attached as Exhibit B. Conversion to a fucosylation product is demonstrated by the reduction in intensity of the '2SA 0 Fuc' and '1SA 0 Fuc' band. As reported in the O-linked glycan results of SFZ:

> Native material is about 50% sialylated, and contains none of the correct sialyl Lewis x glycan. In vitro sialylation as well as fucosylation appear to be quantitative with the desired structure generated at well over 90% of total O-linked glycans. Remodeled material is fully active.
>
> Exhibit B, lines 15-18.

These results are part of a collaboration which was disclosed by Dr. David Zopf in paragraph 7, and Exhibits F and G, of his Declaration filed on December 9, 2004. A copy of this declaration and the relevant Exhibits accompanies this Response.

Additional evidence of enablement involving FucT-VI is demonstrated experimentally by Exhibit C. Exhibit C is a declaration from Dr. Robert Bayer which was originally presented in the Response to the Third Office Action filed on December 9, 2004. By following the *in vitro* fucosylation method taught by the present invention, a research group including the inventors of the present invention successfully demonstrated the use of soluble human FucT-VI, *i.e.*, FucT-VI without the transmembrane domain to produce a therapeutic peptide (complement inhibitor) with a substantially uniform fucosylation pattern. This achievement was published in the scientific journal, *Glycobiology*, and is described in Example 1 of the application.

In addition to having their efficacy demonstrated experimentally, the claimed methods are also supported by the specification. Explicit support for the preferred use of FucT-VI and FucT-VII is provided in the following passages:

> In other embodiments, fucosyltransferases for use in the methods of the invention include FucT-VII and FucT-VI. Each

> of these enzymes preferably catalyzes the fucosylation of at least 60% of their targeted glycopeptide-linked fucosyltransferase acceptor sites present in a population of glycopeptides.
>
> As most of the studies on *in vitro* fucosylation to date have focused on the fucosylation of small molecule substrates, the art has not recognized any substantial difference between the efficiency of fucosylation of the various fucosyltransferases. The inventors have, however, discovered that certain FucT molecules are surprisingly more effective at fucosylating glycopeptides. For example, FucT-VI is approximately 8-fold more effective at fucosylating glycopeptides than is FucT-V. Thus, in a preferred embodiment, the invention provides a method of fucosylating an acceptor on a glycopeptide using a fucosyltransferase that provides a degree of fucosylation that is at least about 2-fold greater, more preferably at least about 4-fold greater, still more preferably at least about 6-fold greater, and even more preferably at least about 8-fold greater than is achieved under identical conditions using FucT-V. Presently preferred fucosyltransferases include FucT-VI and FucT-VII.
>
> Specification, p. 27 line 5 to p. 28 line 2.

These passages from the specification clearly recite the preferred use of FucT-VI and FucT-VII in the methods of the invention.

The specification further describes other examples of fucosyltransferases suitable for the present invention including βGal(1→4)βGlcNac α(1→3)fucosyltransferases (FucT-VI, FucT-VII, E.C. No. 2.4.1.65). See page 26 lines 8-12 in the specification. The specification also provides a table of exemplary fucosyltransferases useful for *in vitro* methods of the present invention including FucT-VI and VII along with their respective tissue distribution patterns, substrates, and products.

In addition, the specification teaches that fucosyltransferases of the present invention can lack the membrane anchoring domain. See page 12, lines 10-15 in the specification. As acknowledged by the Examiner in the Office Action, fucosyltransferases and sequence information for fucosyltransferases are known and available in the art. One skilled in the art can readily identify the stem region, trans-membrane region and the C-terminal region of a given fucosyltransferase based on its amino acid sequence information, *e.g.,* via

hydropathy plots. See also page 443-444 Molecular Biology of the Cell, second edition published by Garland Publishing, Inc. A copy of which is attached as Exhibit A. Therefore, one skilled in the art can easily identify and delete the membrane anchoring domain, *i.e.*, the trans-membrane region of a fucosyltransferase for it to be used in the present invention.

In addition, Example 4 demonstrates that additional fucosyltransferases useful for the present invention can be readily identified by using a simple radiolabeling method widely used in the field. Specifically a tracer amount of radiolabeled GDP-fucose can be added to a fucosylation reaction, which can be subsequently used to determine the amount of fucose incorporated into a protein, *e.g.*, by quantifying the radioactivity using an in-line scintillation detector.

In summary, the specification clearly teaches that FucT-VI, FucT-VII, and combinations thereof can be used *in vitro* to provide a substantially uniform fucosylation pattern for glycopeptides. The specification enumerates a sufficient number of readily available fucosyltransferases including preferred fucosyltransferases that can be useful for the methods provided by the present invention. The specification also provides ample examples to demonstrate the operability and success of the claimed methods achieved by following the teaching and guidance provided by the present invention. In addition, the Wyeth and Avant studies directed to obtaining uniform fucosylation patterns via practicing the methods taught by the present invention is a further validation of the enabling teaching provided by the present invention.

In the Office Action, the Examiner states that fucosyltransferases have a characteristic nature of altogether losing their specific ability to transfer fucose when the transmembrane domain is removed. (Page 4, lines 17-21). Applicants disagree: they have provided experimental examples demonstrating the efficacy of transmembrane domain lacking FucT-VI and FucT-VII. In light of this evidence, it cannot be said that an inability to transfer fucose upon transmembrane domain removal is characteristic. If the Examiner's objection rests on the allegation that the claims encompass a fucosyltransferase which is unable to fucosylate glycopeptides upon removal of its transmembrane domain, then this objection is

misplaced. Inoperative embodiments are permissible in claims. Their presence alone within a claimed method neither renders the claims invalid, nor precludes patentability. Atlas Powder v. E.I. duPont de Nemours, 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984).

Over 35 U.S.C. §112, first paragraph, written description

Claims 1-4, 6, 8, 10-17, 19-21, 31-36, 38, 40, 42-49, 51-53, 66-68, 70-77, 79-86 and 94 are rejected under 35 U.S.C. § 112, first paragraph for alleged lack of written description. The Examiner states the specification does not convey the Applicant's possession of the claimed invention to one of skill in the art. Claims 66-68, 70-77, 79-86 and 94 are cancelled. Applicants have amended the claims and therefore traverse this rejection.

The Examiner is contending that the claims lack written description because peptide sequences of the fucosyltransferases have not been provided in the application. The exact same written description rejection was put forward in an Office Action dated June 9, 2004. Applicants filed a response to this written description requirement on December 9, 2004. In the subsequent Office Action dated March 15, 2005, the Examiner withdrew the rejection, stating

> Applicants' amendments and arguments filed on 12-9-04, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Specifically [*sic*] Examiner has withdrawn the rejections under 35 U.S.C. § 112, 1st paragraph in view of the persuasive arguments presented by the Applicant.
>
> U.S. Pat. App. 09/855,320 Office Action dated March 14, 2005 Page 2, third paragraph

Now the withdrawn rejection from the June 9, 2004 Office Action has been raised again. Applicant is surprised by this. Not only because it conflicts with Patent Office policy, but also because the Examiner has not explained why the "persuasive arguments" from December 9 are now unconvincing. Since the specification has not been amended in the interim, it cannot be through any changes in the underlying application. Applicants have reprinted the

persuasive arguments, attached them as Exhibit D, and respectfully request an explanation for this change. If there is no explanation, then Applicants respectfully request permanent withdrawal of this rejection.

Over 35 U.S.C. §103(a)

Over Kashem and Paulson

Claims 54-55, 87-93, 95-106 are rejected under 35 U.S.C. § 103(a) for alleged obviousness over the combination of Kashem et al. (U.S. Pat. No. 5,374,655) ("Kashem") and Paulson, *et al.*, (PCT Publication No. 98/31826) ("Paulson"). Claims 90, 92 and 103 are cancelled. Applicants traverse.

A *prima facie* obviousness rejection based on the combined teachings of Kashem and Paulson can not be raised because there is a lack of motivation to combine these two references. In order to combine, there must be some suggestion, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or the combine reference teachings. MPEP 2143. A statement that modifications of the prior art to meet the claimed invention would have been "well within the ordinary skill of the art at the time the claimed invention was made" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a prima facie case of obviousness without some objective reason to combine the teachings of the references. MPEP 2143.01(IV).

Therefore, in order to combine, there must be some reason for someone reading Paulson to look to Kashem to perform Applicant's invention, or vice versa. This motivation is simply not present.

Paulson, for example, does not provide this motivation. In the instant Office Action, Paulson is cited by the Examiner for "essentially teach[ing] a method of glycosylation involving an enzyme other than a fucosyltransferase". In an earlier Office Action dated March 15, 2005, the Examiner describes Paulson as "show[ing] the availability of methods to glycosylate peptides using enzymes other than FT [fucosyltransferases] was well known in the

art. This reference [Paulson] was used in order to address claim limitations such as glycosylation by an enzyme other than an FT." (page 7, lines 5-8)

The Examiner appears to state that the methods of Paulson can be applied to enzymes other than sialyltransferases. However, this conclusion can not be drawn from Paulson itself. Paulson does not teach or remotely suggest the applicability of its methods beyond sialyltransferases for any other saccharide or glycosyltransferase. Paulson's methods are discussed specifically within the context of sialylation or their use with sialyltransferases; the disclosure does not describe, for example, fucosyltransferases or methods of adding fucose to a glycoprotein. Since Paulson's teachings do not extend beyond sialylation, it is improper to characterize Paulson as "essentially teach[ing] a method of glycosylation involving an enzyme other than a fucosyltransferase". Rather, Paulson teaches a method of sialylation involving sialyltransferases.

The motivation to combine is also lacking in Kashem. Kashem describes methods of both monofucosylating and sialylating a substrate. Since both types of enzymatic reactions are taught in Kashem, one would expect a discussion of the interchangeability of the methods to be included in Kashem if it were possible. However, there is no such discussion in Kashem. Kashem does not teach or suggest that methods of sialylation can be successfully applied to methods of fucosylation.

In summary, Applicants have demonstrated that a motivation to combine Kashem and Paulson is not present in either reference. The Examiner has not provided any evidence in the literature to support a claim that the interchangeability of sialylation and fucosylation conditions are part of the general knowledge of one of skill in the art. The only document which links Paulson and Kashem is the Applicant's patent application. When the Applicant's patent application is the sole basis for the construction of an obviousness rejection, impermissible hindsight has been used. MPEP § 2141.01(III). Therefore, a motivation to combine, an essential element of obviousness, has not been made. Applicants respectfully request withdrawal of this rejection.

In an Office Action dated March 15, 2005, the Examiner states that Paulson can also address claim limitations such as glycosylation by an enzyme other than a FT. While this statement is not part of a current rejection, it is appropriate to mention earlier statements concerning Paulson at this time. In the current claim set, there are no claim limitations directed to glycosylation by an enzyme other than a FT, thus rendering this argument moot.

Over Seed and Paulson

Claims 54-55, 87-93, 95-106 are rejected under 35 U.S.C. § 103(a) for alleged obviousness over the combination of Seed, *et al.*, (PCT Publication No. 96/40881) ("Seed") and Paulson. Claims 90, 92, 103, 105 and 106 are cancelled. Applicants traverse.

As mentioned in the response to the rejection over Kashem and Paulson, a motivation to combine is essential for constructing an obviousness rejection. Therefore, in order to combine Seed and Paulson, there must be some reason for someone reading Paulson to look to Seed to perform Applicant's invention, or vice versa. This motivation is simply not present.

As mentioned above, Paulson does not state that its sialylation methods are applicable for other transferases, such as fucosyltransferases. This motivation to combine is also not provided by Seed. Seed discloses the DNA and amino acid sequences of $\alpha(1,3)$fucosyltransferase and the use of such full length fucosyltransferases for fucosylation of therapeutic peptides. However, Seed does not teach or suggest that methods of sialylation can be successfully applied to methods of fucosylation. Therefore, Seed also does not provide the motivation to combine.

In summary, Applicants have demonstrated that a motivation to combine Seed and Paulson is not present in either reference. The Examiner has not provided any evidence in the literature to support a claim that the interchangeability of sialylation and fucosylation conditions are part of the general knowledge of one of skill in the art. The only document which links Paulson and Seed is the Applicant's patent application. When the Applicant's patent application is the sole basis for the construction of an obviousness rejection, impermissible hindsight has been used. MPEP § 2141.01(III). Therefore, a motivation to

combine, an essential element of obviousness, has not been made. Applicants respectfully request withdrawal of this rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Applicants respectfully request a telephone interview if the Examiner believes that the claims as amended are not in condition for allowance in light of the response submitted above. The undersigned can be reached at 415-442-1000.

Respectfully submitted,

Todd Esker
Reg. No. 46,690

MORGAN, LEWIS & BOCKIUS, LLP
One Market, Spear Street Tower
San Francisco, California 94105
Tel: 415-442-1000
Fax: 415-442-1001
Attachments
1-SF/7394008.4

EXHIBIT I

GLYCO-REMODELING OF rPSGL-Ig DRUG SUBSTANCE: RESULTS FROM FEASIBILITY STUDIES CONDUCTED IN COLLABORATION WITH NEOSE TECHNOLOGIES, INC.

[May 24, 1999 – March 31, 2000]

Date: March 31, 2000

Prepared by:

Martin S. Sinacore, Ph.D.
Drug Substance Development/Cell & Molecular Science
Genetics Institute

and

Mark R. Hardy, Ph.D.
Biopharmaceutical Characterization & Analysis
Genetics Institute

General Background

Feasibility studies designed to evaluate the *in vitro* glyco-remodeling of rPSGL-Ig drug substance using technology developed at Neose Technologies, Inc. were performed between May 24, 1999 and March 31, 2000. The intent of the studies was to establish the efficacy of *in vitro* sialylation and fucosylation reactions in improving the proportion of O-linked rPSGL-Ig oligosaccharide bearing the sialyl Lewis^x determinant. Accordingly, preparations of rPSGL-Ig drug substance (designated as FFA62 & SFZ) shown to be hypofucosylated and hyposialylated to different degrees were provided to Bob Bayer of Neose Technologies, Inc. for *in vitro* glyco-remodeling. Remodeled rPSGL-Ig preparations were returned to Genetics Institute for both functional and biochemical characterization.

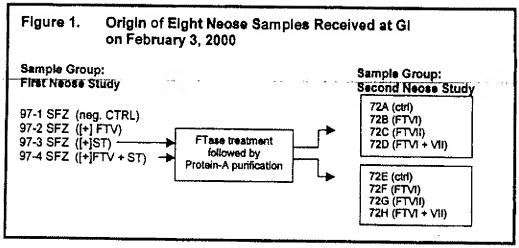
The goals of the feasibility studies were twofold:

1. To demonstrate the effectiveness of glycoprotein remodeling technology on rPSGL-Ig protein, and
2. To learn more about the impact of the extent of oligosaccharide fucosylation and sialylation on the *in vitro* P-Selectin binding activity of rPSGL-Ig.

RESULTS FROM THE SECOND FEASIBILITY STUDY

All four SFZ-derived rPSGL-Ig samples arising from the first Neose reglycosylation feasibility experiment (97-1, 97-2, 97-3 & 97-4) were returned to Neose on November 29, 1999 for additional treatment with FTVI and/or FTVII. Neose then performed some development experiments, guided by our provision of the SOP AN080 method for O-linked oligosaccharide alditol HPAEC/PED fingerprinting. Eight samples were then received at GI from Neose on February 3, 2000, for our analysis. The history of the eight Neose samples arising from their second round of experiments is given in Fig. 1. In a letter dated February 22, 2000 Neose subsequently provided HPAEC/PED O-glycan alditol fingerprint data suggesting that the second round of FTase experiments had been successful in adding outerbranch fucose to SFZ O-glycans. GI initially evaluated the "quality" of the eight samples by SEC-HPLC (to assess the amount of high molecular weight species present) and by the *in vitro* activity "RBU" assay.

Figure 1. Origin of Eight Neose Samples Received at GI on February 3, 2000



Levels of rPSGL-Ig high molecular weight species in the eight new samples were low and similar to the levels originally observed for SFZ material. SEC-HPLC of the eight samples revealed a "late shoulder" in some of the second set (i.e., 72E through 72H) samples (data not shown). This has been shown to correlate to samples treated with FTV in the first round of Neose experiments, although its identity is unknown. Efforts to identify the material appearing in the "late shoulder" fraction are underway.

The P-selectin binding activity of these samples was examined and the results are shown in Table 1. The control samples 72A and 72E showed very low levels of *in vitro* activity consistent with the original RBU results for samples SFZ 97-3 and 97-4 (see Attachment #2 of the addendum). SFZ samples treated with FT VI and/or FT VII, however, showed an increase in RBU activity similar to that of the current rPSGL-Ig reference material. These results were the first indication that *in vitro* glyco-remodeling of rPSGL-Ig could restore P-selectin binding activity in previously inactive SFZ rPSGL-Ig material.

Table 1:
P-Selectin Binding Activity of Glyco-Remodeled rPSGL-Ig

Sample	RBU
Ref.material, 8H25K903	By definition, 1.0
72A	0.12
72B	0.88
72C	0.98
72D	1.2
Ref. material, 8H25K903	By definition, 1.0
72E	0.34
72F	0.98
72G	0.96
72H	1.12

The O-glycan alditol fingerprint analysis provided by Neose indicated that all of the FT Vi and/or FT VII - treated samples showed marked conversion to the desired fucosylated, disialylated Core 2 structure. The HPAEC-PED O - glycan fingerprint analysis of the same rPSGL-Ig samples was repeated at GI. The results shown in Table 3 indicated that treatment of rPSGL-Ig with either FTVI or FTVII led to conversion of O-linked glycans to fully sialylated & fucosylated species. Therefore the restoration of P-selectin binding activity correlated with the appearance of core 2 oligosaccharides bearing the SLe^X determinant.

Table 3:
HPAEC-PED O-Linked Glycan Analysis of Glyco-Remodeled rPSGL-Ig

	% Disialylated Species (GI)		% Disialylated Species (Neose)	
Sample ID	2SA_1Fuc	2SA_0Fuc	2SA_1Fuc	2SA_0Fuc
Ref standard	40	60		
72A	14	86	19	81
72B	100	0	80	20
72C	100	0	78	22
72D	100	0	83	17
72E	26	74	30	70
72F	100	0	80	20
72G	100	0	75	25
72H	100	0	80	20

Although the results of the second feasibility study were very encouraging we wished to repeat the study to test the reproducibility of the glyco-remodeling process. In addition, given that the samples generated in second feasibility study had been exposed to the action of both FTV and, in the second round, to FTVI & FTVII (alone or in combination) we wanted to see if the outcome might be different if the glyco-remodeling reactions were run on material that had not been previously exposed to either sialyltransferase or fucosyltransferase. Accordingly, at our request Bob Bayer repeated the enzymatic treatments on rPSGL-Ig SFZ sample that was not exposed to transferase enzymes (97-1 control sample from the first feasibility study). Due to the relatively small amount of total rPSGL-Ig protein remaining in the 97-1 sample (~4mgs), only the sialyltransferase and FTVI treatments were performed.

The P-selectin binding activity of the glyco-remodeled 97-1 rPSGL-Ig material (designated as 138-1) was compared to a untreated control sample. The results indicated that the 138-1 sample had a significantly elevated RBU relative to control. Although the RBU value of 0.75 is within the variability of the values seen historically for the reference material, the combination of the differences seen by parallel line analysis (data not shown) and the lower RBU value suggest the 138-1 material is not as active as the reference material. The significance of this result will await further testing and evaluation of glyco-remodeled rPSGL-Ig preparations.

Table 4:
P-Selectin Binding Activity of Glyco-Remodeled 97-1 rPSGL-Ig Sample

Sample	RBU
Ref.material, 8H25K903	By definition, 1.0
Control	0.09
138-1	0.75

SUMMARY AND CONCLUSIONS

Two feasibility studies designed to evaluate the efficacy of in vitro glyco-remodeling technology on rPSGL-Ig structure and function have been carried out in collaboration with Neose Technologies, Inc. The results of these studies indicate that rPSGL-Ig can be successfully glyco-remodeled using sialyltranserase and fucosyltransferase VI or VII. Using this combination of transferase incubations the P-selectin binding activity of a previously inactive rPSGL-Ig drug substance preparation was completely restored. The restoration of binding activity correlated with the conversion of core 2 O-linked glycan structures to the desired fucosylated, disialylated form. Therefore, the first goal of the feasibility studies (*to demonstrate the effectiveness of glycoprotein remodeling technology on the rPSGL-Ig protein)* has been met. However, the second goal of the feasibility (*to learn more about the impact of the extent of oligosaccharide fucosylation and sialylation on the in vitro P-Selectin binding activity of rPSGL-Ig*) has not been met. While the data we have thus far suggests that more complete sialylation of rPSGL-Ig reference material did not improve *in vitro* P-selectin binding activity, the effect of more complete fucosylation has not been determined.

Therefore, further evaluation of the Neose glyco-remodeling technology is warranted. We would propose that follow-up studies examine;

a) The effect of sialyltransferase and fucosyltransferase VI (alone & in combination) on the P-selectin binding activity of rPSGL-Ig reference material (or equivalent) and SFZ material. We would propose that these studies be done with appropriate rPSGL-Ig In-process intermediates (e.g. Protein-A eluates).
b) The biological properties of glyco-remodeled rPSGL-Ig in relevant *in vitro* & *in vivo* assays.

Finally, looking forward, we will need information regarding, 1) the cost and availability of transferase & substrate reagents, 2) the quality of recombinant transferase reagents and 3) methods appropriate for tracking the removal of transferases (and transferase substrates) in the downstream rPSGL-Ig purification process.

EXHIBIT II

Kathryn Gregory

From: Bob Bayer [bbayer@neose.com]
Sent: Wednesday, December 06, 2000 3:48 PM
To: kgregory@neose.com
Subject: GI


Enbrel Summary.doc


rPSGL Ig Summary.doc

Kathryn,

The GI dates are:

May 24, 1999 initial meeting
August 12, 1999 samples shipped to me, remodeled with FTV
September 15, 1999 samples returned to GI
November 1, 1999 GI report on FT V remodeled samples
November 29, 1999 samples returned to me for remodeling with FTVI, FTVII
February 2, 2000 samples returned to GI
March 31, 2000 meeting with GI
May 30, 2000 GI announces new rPSGL-Ig ready, preference for FTVII
July 17, 2000 samples arrive for remodeling with ST3Gal3, FTVII
August 17, 2000 samples returned to GI

Also, enclosed is the information that I sent to Steve.

Bob

rPSGL Ig Summary:

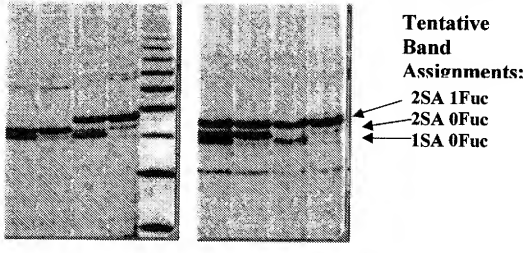
The P-selectin glycoprotein ligand Ig chimera rPSGL-Ig) is currently produced by Genetics Institute in CHO cells transfected with ooth N-acetyl-D-glucosaminyl-transferase (core 2 transferase) and FTVII. The molecule contains two N-linked, and 6-7 O-linked sites per monomer. Only one O-linked site near sulfated tyrosines is critical for bioactivity.

The expression level with the current cell line is low enough that generating material for Phase III and market is durficult. GI would like to switch to a high expressing cell line which would enable them to expand the number of indications they can market the drug for.

Remodeling: The SFZ cell line is the high expressor used to generate the protein sent to Neose for remodeling. As is, it is inactive. Both the SFZ cell line and the current producer cell line (FFA62) were sent to Neose for either sialylation, fucosylation, or sialylation plus fucosylation.

SFZ O-linked glycan results: Native material is about 50% sialylated, and contains none of the correct sialyl Lewis x glycan. In vitro sialylation as well as fucosylation appear to be quantitative with the desired structure generated at well over 90% of total O-linked glycans. Remodeled material is fully active.

rFA62 O-linked glycan results: Glycan analysis of total O-linked glycans from the "active" material shows both undersialylated as well as underfucosylated glycoforms present in similar abundance to the desired sialyl Lewis x glycoform. After sialylation and fucosylation, the desired glycan is generated quantitatively, as with the SFZ cell line



SFZ:
Native
+SA
+Fuc
+SA,Fuc

FFA62:
Native
+SA
+Fuc
+SA.Fuc

Summary: The high producing cell line (SFZ or future replacement) combined with Neose technology can produce a fully active product eliminating a production bottleneck and expanding potential markets.

EXHIBIT III

PATENT
Attorney Docket No. 040853-01-5108-US
Client Ref. No.: NEO00073

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation Number: 1113
Robert Bayer	Examiner: Rao, Manjunath
Application No.: 09/855,320	Technology Center/Art Unit: 1652
Filed: May 14, 2001	DECLARATION OF DAVID ZOPF UNDER 37 C.F.R. §1.132
For: IN VITRO MODIFICATION OF GLYCOSYLATION PATTERNS OF RECOMBINANT GLYCOPEPTIDES	
Customer No.: 43850	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, David A. Zopf, M.D. declare as follows:

1. I am Executive Vice President and Chief Scientific Officer of Neose Technologies, Inc. Prior to joining Neose, I was Vice President and Chief Operating Officer of BioCarb, Inc. In addition, I am a former editorial board member of *Archives of Biochemistry and Biophysics*. My *Curriculum Vitae* is attached.

2. I am submitting this declaration to testify for the initial expert skepticism and subsequent commercial success associated with the *in vitro* fucosylation methods provided by the present application.

3. Attached as Exhibit E is a copy of a letter from Professor Dr. James E. Bailey, Institute of Biotechnology, ETH-Zürich, CH-8093 Zurich, Switzerland. In my opinion, the attached letter is an representative example of expert skepticism in the field towards *in vitro* fucosylation methods, especially large scale production provided by the present application.

4. In general, the letter expresses disbelief that an *in vitro* glycosylation process, such as the presently claimed fucosylation process, is commercially viable. Dr. Bailey states that "the process complications and costs associated with producing and utilizing a glycosyltransferase and donor substrate make the exogenous manipulation of glycosylation far less attractive than engineering the cells to maximize the production of the desired glycoform." Dr. Bailey continues by saying, "[f]ailure of much simpler cofactor-requiring enzyme catalyzed reactions to gain industrial success in competition with whole-cell biocatalysts speaks very strongly in my opinion *against* the competitive prospects of *in vitro* remodeling of glycosylation." [Emphasis added].

5. In addition to the foregoing skepticism by experts in the field, the technology, both for *in vitro* glycosylation in general and for *in vitro* fucosylation in particular, has enjoyed commercial success.

6. In my capacity as Executive Vice President and Chief Scientific Officer (and in my previous capacity as Vice President of New Product Development) of Neose, I have directly participated in negotiating agreements with several companies in order to assess the feasibility of our GlycoAdvance fucosylation technology (*in vitro* fucosylation) with recombinant therapeutic glycoproteins in development. Although most of these agreements are subject to non-disclosure agreements which prevent me from disclosing our studies, I am at liberty to disclose two licensing agreements involving our GlycoAdvance fucosylation technology.

7. The first GlycoAdvance fucosylation agreement was with Wyeth/Ayerst Laboratories, the pharmaceutical division of American Home Products. Under this agreement, we employed our GlycoAdvance fucosylation technology for an improved production system for Wyeth's inflammation/thrombosis P selectin antagonist, rPSGL-Ig. We have successfully provided highly fucosylated peptides of Wyeth using the *in vitro* fucosylation methods provided by the present invention. Due to disappointing Phase II clinical trial results, however, the clinical development of this compound was suspended. Please note that Neose's contribution to this technology was successful, and the compound development was suspended for other reasons

that were unrelated to GlycoAdvance. Press releases from Neose announcing both the initiation and suspension of the Wyeth relationship are included as Exhibit F and Exhibit G, respectively.

8. The second GlycoAdvance fucosylation agreement was with Avant Immunotherapeutics. Under this agreement, we employed our GlycoAdvance fucosylation technology for an improved production system for Avant's complement system inhibitor, sCR1-sLe^x. This collaboration was successful, meaning that our GlycoAdvance fucosylation technology was able to consistently fucosylate Avant's target molecule. The results of this collaboration were published this year (Thomas, L.J. *et al.*, *Glycobiology* **14(10)**: 883-893 (2004)). This paper is included as Exhibit B.

9. These two specific *in vitro* fucosylation examples are part of the larger success of Neose's *in vitro* glycosylation strategies. In my capacity as Executive Vice President and Chief Scientific Officer (and in my previous capacity as Vice President of New Product Development) of Neose, I have been directly involved in negotiating agreements with more than 20 companies in order to assess the feasibility of *in vitro* glycosylation technology for recombinant therapeutic glycoproteins in development. All feasibility studies completed to date have been successful. Many of these successful feasibility studies have led to ongoing negotiations for commercial licenses to the technology for large-scale manufacture of human glycoprotein therapeutics. In addition, the present technology is being employed as an essential part of ongoing collaborative research and development agreements with other companies to develop commercial manufacturing methods for cancer vaccines and treatments for neurological diseases. Press releases relating to this are noted in Exhibit H.

10. In my opinion, this commercial success is directly related to the innovative *in vitro* fucosylation methods provided by the present invention and also reflects the long felt needs and failure by others in the field.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so

made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 7 Dec 2004

David A. Zopf, M.D.

CURRICULUM VITAE

David A. Zopf, M.D.

Citizenship United States

Social Security # 493-44-7185

Present Address Neose Technologies, Inc.
102 Witmer Road
Horsham, PA 19044
Phone (215) 441 5890
Fax (215) 441 5896

Education

1964 - A.B., Washington University, St. Louis, MO (Zoology Major)
1969 - M.D., Washington University School of Medicine, St. Louis, MO

Board Certification Anatomic Pathology, 1976

Brief Chronology of Employment

2000 – present	Vice President, New Product Development Neose Technologies, Inc., Horsham,
1992- 2000	Vice President, Drug Development Neose Technologies, Inc., Horsham, PA
1988-1991	Vice President and Chief Operating Officer, BioCarb Inc, Gaithersburg, MD
1982-1988	Chief, Section on Biochemical Pathology Division Cancer Biology and Diagnosis, National Cancer Institute, National Institutes of Health, Bethesda, MD
1977-1981	Expert Consultant, Laboratory of Pathology, Division Cancer Biology and Diagnosis, National Cancer Institute, National Institutes of Health, Bethesda, MD
1974-1977	Senior Staff Fellow, Laboratory of Biochemical Pharmacology, National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Bethesda, MD
1971-1974	Clinical Associate, Laboratory of Biochemical Pharmacology, National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Bethesda, MD

1970-1971	Resident, Anatomic Pathology, Department of Pathology, University of Colorado School of Medicine, Denver, CO
1969-1970	Resident, Anatomic Pathology, Department of Pathology, New York University, Bellevue Medical Hospital, NY
Military Service	Active duty July 1971-1974; 1981-1988 Commissioned Corps, U.S. Public Health Service, National Institutes of Health, Bethesda, MD
Societies	American Association for the Advancement of Science Society for Glycobiology Pluto Club (emeritus) American Association of Pathologists American Society of Biochemistry and Molecular Biology American Chemical Society
Editorial Boards	Archives Biochemistry and Biophysics, Section on Immunochemistry and Complex Carbohydrates Experimental Pathology Glycoconjugate Journal (1984 - 1991)
Research Interests	Immunochemistry of complex carbohydrates Biochemistry of human blood groups Immune responsiveness to complex carbohydrates Structure, function, and biosynthesis of tumor-associated antigens Affinity methods for analysis of complex carbohydrates Development of oligosaccharide anti-infective drugs

1. Kinsky, S.L., Luse, S.A., Zopf, D.A., van Deenen, L.L.M., and Haxby, J.: Interaction of filipin and derivatives with erythrocyte membranes and lipid dispersions: electron microscopic observations. Biochem. Biophys. Acta 135: 844-861, 1967.

2. Kinsky, S.C., Haxby, J.A., Zopf, D.A., Alving, C.R., and Kinsky, C.B.: Complement-dependent damage to liposomes prepared from pure lipids and Forssman hapten. Biochemistry 8: 4149-4158, 1969.

3. Zopf, D.A.: Electron microscopic and osmotic studies on the effect of polyene antibiotics upon natural and artificial membranes. Borden Award Thesis, Washington University School of Medicine, 1969.

4. Zopf, D.A., and Ginsburg, V.: Carbohydrate antigens of cell surfaces. In Lee, E.Y.C. and Smith, E.E. (Eds.): Biology and Chemistry of Eucaryotic Cell Surfaces. New York, Academic Press, 1974, vol. 7, 259-271.

5. Zopf, D.A., and Ginsburg, V.: Solubilization and expression of cell surface components. In Kahan, B.D. and Reisfeld, R.A. (Eds.): The Cell Surfaces. Immunological and Chemical Approaches. New York, Plenum Press, 1974, 51-57. (Adv. Exp. Med. Biol., Vol. 51).

6. Zopf, D.A. and Ginsburg, V.: Preparation of precipitating antigens by coupling oligosaccharides to polylysine. Arch. Biochem. Biophys. 167: 345-350, 1975.

7. Jeffrey, A.M., Zopf, D.A., and Ginsburg, V.: Affinity chromatography of carbohydrate-specific immunoglobulins: coupling of oligosaccharide to Sepharose. Biochem. Biophys. Res. Commun. 62: 608-613, 1975.

8. Zopf, D.A., Ginsburg, A., and Ginsburg, V.: Goat antibody directed against a human Leb blood group hapten, lacto-N-difucohexaose I. J. Immunol. 115: 1525-1529, 1979

9. Ginsburg, V., Zopf, D.A., Yamashita, K., and Kobata, A.: Oligosaccharides of human milk: Isolation of a new pentasaccharide, lacto-N-fucopentaose V. Arch. Biochem. Biophys. 175: 565-568, 1976.

10. Tsai, C.M., Zopf, D.A., Yu, R.K., Wistar, R., Jr., and Ginsburg, V.: A human cold agglutinin specific for lacto-N-neotetraose. J. Immunol. 117: 717-721, 1976.

11. Tsai, C.-M., Zopf, D.A., Yu, R.L., Wistar, R., Jr., and Ginsburg,V. A Waldenstrom macroglobulin that is both a cold agglutinin and a cryoglobulin because it binds N-acetylneuraminosyl residues. Proc. Natl. Acad. Sci. USA 74: 4591-4594, 1977.

12. Zopf, D.A., Tsai, C.-M., and Ginsburg, V. Studies on the carbohydrate receptors of cold agglutinins using synthetic antigens. In Mohn, J.F., Plunkett, R.W., Cunningham, R.K., and Lambert, R.M. (Eds.): Human Blood Groups. Basel,Switzerland, S. Karger AG, 1977, pp. 172-178.

13. Zopf, D.A., Tsai, C.-M., and Ginsburg, V. Antibodies against oligosaccharides coupled to proteins: Characterization of carbohydrate specificity by radioimmune assay. Arch. Biochem. Biophys. 185: 61-71, 1978.

14. Tsai, C.-M., Zopf, D.A., and Ginsburg, V. The molecular basis for cold agglutination: Effect of receptor density upon thermal amplitude of a cold agglutinin. Biochem. Biophys. Res. Commun.80: 905-910, 1978.

15. Smith, D.F., Zopf, D.A., and Ginsburg, V. Fractionation of sialyl oligosaccharides of human milk by ion-exchange chromatography. Anal. Biochem. 85: 602-608, 1978.

16. Zopf, D.A., Tsai, C.-M., and Ginsburg, V. Carbohydrate antigens: coupling of oligosaccharide-phenethylamine derivatives to edestin by diazotization and characterization of antibody specificity by radioimmunoassay. In Ginsburg, V.(Ed.): Methods in Enzymology. New York, Academic Press, 1978, Vol. L, pp. 163-169.

17. Zopf, D.A., Drzeniek, Z., Smith, D.F., Tsai, C.-M., and Ginsburg, V. Carbohydrate antigens: affinity purification of antibodies using oligosaccharide-phenethylamine derivatives coupled to Sepharose. In Ginsburg, V. (Ed.): Methods in Enzymology. New York, Academic Press, 1978, Vol. L, pp. 171-175.

18. Smith, D.F., Zopf, D.A., and Ginsburg, V. Carbohydrate antigens: Coupling of oligosaccharide-phenethylamine-isothiocyanate derivatives to bovine serum albumin. In Ginsburg, V. (Ed.): Methods in Enzymology. New York, Academic Press, 1978, Vol. L, pp. 169-171.

19. Smith, D.F., Zopf, D.A., Ginsburg, V. Sialyl oligosaccharides from milk. In Ginsburg, V.(Ed.): Methods in Enzymology. New York, Academic Press, 1978, Vol. L, pp. 221-226.

20. Zopf, D.A., Tsai, C-M., and Ginsburg, V. Antibodies against oligosaccharides. In Goldstein, I.J., (Ed.): Carbohydrate-Protein Interaction. Washington, D.C., American Chemical Society, 1979, pp. 90-101.

21. Zopf, D.A., Ginsburg, V., Hallgren, P., Johnson, A.C., Lindberg, B.S, and Lundblad, A. Determination of Le^b-active oligosaccharides, in urine of pregnant and lactating women by radioimmunoassay. Eur. J. Biochem. 93: 431-435, 1979.

22. Rohr, T.E., Smith, D.F., Zopf, D.A., and Ginsburg, V. Le^b-active glycolipid in human plasma: measurement by radioimmunoassay. Arch. Biochem. Biophys. 199: 265-269, 1980.

23. Ginsburg, V., McGinniss, M.M., and Zopf, D.A. Biochemical basis for some blood groups. In Sandler, S.G., Nusbacher, J., and Schanfield, M.S., (Eds.): Immunobiology of the Erythrocyte. New York, Alan R. Liss, Inc., 1980, pp. 45-53.

24. Warner, C.V, Smith, D.F., Zopf, D.A., and Ginsburg, V. A human Le(a-b+) blood group agglutinin prepared by polymerizing goat anti-lacto-N-difucohexaose I IgG. Molec. Immunol. 17:1163-1166, 1980.

25. Hammar, L., Mansson, S., Rohr, T., Chester, M.A., Ginsburg, V., Lundblad, A., and Zopf, D.A.: Decreased expression of the Le^b antigen during pregnancy: Determination of erythrocyte agglutinability and Le^b-active glycolipid in serum. Vox Sang. 40: 27-33, 1981.

26. Zopf, D.A, Levinson, R.E., and Lundblad, A. Determination of a glucose-containing tetrasaccharide in urine by radioimmunoassay. J. Immunol. Meth. 48: 109-119, 1982.

27. Stein, K.E., Zopf, D.A., Johnson, B.M., Miller, C.B., and Paul, W.E. The immune response to an isomaltohexosyl-protein conjugate, a thymus-dependent analogue of (α1-6)dextran. J. Immunol. 128: 1350-1354, 1982.

28. Nilsson, B., and Zopf, D.A. Gas chromatography and mass spectrometry of hexosamine-containing oligosaccharide alditols as their permethylated, N-trifluoroacetyl derivatives. In Ginsburg, V. (Ed.): Methods in Enzymology. New York, Academic Press, 1982, Vol. 83, pp. 46-58.

29. Magnani, J.L., Nilsson, B., Brockhaus, M., Zopf, D.A., Steplewski, Z., Koprowski, H., and Ginsburg, V. A monoclonal antibody-defined antigen associated with gastrointestinal cancer is a ganglioside containing sialylated lacto-N-fucopentaose II. J. Biol. Chem. 257: 14365-14369, 1982.

30. Stein, K.E., Zopf, D.A., Miller, C.B., Johnson, B.M., Mongini,P.K.A., Ahmed, A., and Paul, W.E. The immune response to a thymus dependent form of B512 dextran requires the presence of lyb5+ lymphocytes. J. Exp. Med. 157: 657-666, 1983.

31. Nilsson, B., and Zopf, D.A.: Oligosaccharides released from glycolipids by trifluoroacetolysis can be analyzed by gas chromatography/mass spectrometry. Arch. Biochem. Biophys. 222: 628-648, 1983.

32. Ugorski, M., Seder, A., Lundblad, A., and Zopf, D. Studies on the metabolic origin of a glucose-containing tetrasaccharide in human urine. J. Exp. Pathol. 1: 27-38, 1983.

33. Rao, A.S., Kabat, E.A., Whittaker, N.F., Nilsson B., Zopf, D.A., and Nimmich,W. Isolation and characterization of a 3,4-pyruvic acetylated-D-galactose-containing oligosaccharide obtained from the capsular polysaccharide of Klebsiella K33 by Smith degradation. Carbohydr. Res. 116: 271-276, 1983.

34. Rao, A.S., Kabat, E.A., Nilsson, B., Zopf, D.A., and Nimmich, W.: Isolation and characterization of a 4-0-[3,4-0-(1-carboxy-ethylidene)-α-D-galactopyranosyl] erythritol from Klebsiella K33 polysaccharide. Carbohydr. Res. 121: 205-209, 1983.

35. Chester, M.A., Lundblad, A., Hager, A., Sjöblad, S., Loonen, C.,Tager, J.M., and Zopf, D.A. Increased urinary excretion of a glycogen-derived tetrasaccharide in heterozygotes with glycogen storage disease type II and III. Lancet No. 8331: 994-995, 1983.

36. Ugorski, M., Nilsson, B., Schroer, K., Cashel, J.A., and Zopf, D. GC/MS analysis of oligosaccharides from neutral glycosphingolipids of murine B cell hybridoma. J. Biol. Chem. 259: 481-486, 1984.

37. Messeter, L., Brodin, T., Chester, M.A., Karlsson, K.-A., Zopf, D.A., and Lundblad, A. Immunochemical characterization of a mono-clonal anti-Leb blood grouping reagent. Vox Sang. 46: 66-74, 1984.

38. Lundblad, A., Schroer, K., and Zopf, D. Radioimmunoassay of a glucose-containing tetrasaccharide using a monoclonal antibody. J. Immunol. Meth. 68:217-226, 1984.

39. Lundblad, A., Schroer, K., and Zopf, D.: Affinity purification of a glucose-containing oligosaccharide using a monoclonal antibody. J. Immunol. Meth. 68:227-234, 1984.

40. Wu, A.M., Kabat, E.A., Nilsson, B., Zopf, D.A., Gruezo, F.G., and Liao, J. Immunochemical studies on blood groups. LXXI. Purification and characterization of radioactive [3H] reduced di- to hexa-saccharides produced by alkaline β-elimination-borohydride [3H] reduction of Smith degraded blood group A active glycoproteins. J. Biol. Chem. 259: 7178-7186, 1984.

41. McGinniss, M.H., Wasniowska, K., Zopf, D.A., Straus, S.E., and Reichert, C.M. An erythrocyte Pr auto-antibody with sialoglycoprotein specificity in a patient with purine nucleoside phosphorylase deficiency. Transfusion 25: 131-136, 1985.

42. Wasniowska, K., Reichert, C.M., McGinniss, M.H., Schroer, K.R., Zopf, D.A. Monoclonal antibodies specific for the blood group N determinant. Glycoconjugate J. 2: 163-176, 1985.

43. Hansson, G.C., and Zopf, D.A. Biosynthesis of the cancer-associated sialyl-Le^a antigen. J. Biol. Chem. 260: 9288-9392, 1985.

44. Kumlien, J., Frejd., T., Magnusson, G., Zopf, D.A., and Lundblad, A. A new non-equilibrium enzyme linked immunosorbent assay for a glycogen-derived urinary tetrasaccharide. Glycoconjugate J. 3: 85-94, 1986.

45. Dakour, J., Hansson, G.C,, Lundblad, A., and Zopf, D.A. Separation and partial sequence analysis of blood group A-active oligosaccharides by affinity chromatography using monoclonal antibodies. Arch. Biochem. Biophys. 248: 677-683, 1986.

46. Nilsson, B., Rosen, S.W., Weintraub, B.D., and Zopf, D.A.: Differences in the carbohydrate moieties of the common subunits of human chorionic gonadotropin, luteinizing hormone, follicle-stimulating hormone, and thyrotropin: Preliminary structural inferences from direct methylation analysis. Endocrinology 119: 2737-2743, 1986.

47. Dakour, J., Lundblad, A., and Zopf, D.A. Separation of blood group A-active oligosaccharides by high-pressure liquid affinity chromatography using a monoclonal antibody bound to concanavalin A silica, Anal. Biochem. 161: 140-143, 1987.

48. Mato, J.M., Kelly, K.L., Alber, A., Jarett, L., Corkey, B.E., Cashel, J.A., and Zopf, D.A. Partial structure of an insulin-sensitive glycophospholipid. Biochem. Biophys. Res. Commun. 146: 764-770, 1987.

49. Brodin, T., Chester, M.A., Karlsson, K.-A., Messeter, L., Zopf, D.A., and Lundblad, A. A monoclonal antibody that recognizes both Leb and Y antigens. Glycoconjugate J. 4: 399-406, 1987.

50. Zopf, D.A., Schroer, K., Hansson, G., Dakour, J., and Lundblad, A.: Affinity purification of oligosaccharides using monoclonal antibodies. Meth. Enzymol. 138: 307-313, 1987,

51. Hansson, G.C., Wasniowski, K., Rock, J.A., Ness, P.M., Kickler, T.S., Shirey, R.S., Neibyl, J.R., and Zopf, D.A.; The glycosphingolipid composition of the placenta of a blood group P fetus delivered by a blood group pk-woman and analysis of the anti-globoside antibodies found in the maternal serum. Arch, Biochem.Biophys. 260: 168-176, 1988.

52. Wasniowska, K., Schroer, K.R., McGinniss, M., Reichert, C,, and Zopf, D.A. Monoclonal antibodies against glycophorin A. Hyridoma 7: 49-54, 1988.

53. Mårtensson, S., Due, C., Nilsson, B., Påhlsson, P,, Ericsson, H., Zopf, D.A., Olsson, L., and Lundblad, A.; A carbohydrate epitope associated with human squamous lung cancer, Cancer Res, 48: 2125-2131, 1988,

54. Dakour, J., Lundblad, A., and Zopf, D.A. Detection and isolation of oligosaccharides with Lea and Leb blood group activities by affinity chromatography using monoclonal antibodies. Arch.Biochem. Biophys. 264: 203-213, 1988.

55. Ohlson, S., Lundblad, A., and Zopf, D.A. Novel approach to affinity chromatography using "weak" monoclonal antibodies. Anal.Biochem. 169: 204-208, 1988.

56. Zopf, D.A., and Hansson, G. The chemical basis for expression of the sialyl-Le^a antigen. In Wu, A. (Ed.): Molecular Immunology ofComplex Carbohydrates. New York, Plenum Press, pp. 657, 1988.

57. Kumlien, J., Chester, M.A., Lindberg, B.S., Pizzo, P., Zopf, D.A. and Lundblad, A. Urinary excretion of a glucose-containing tetrasaccharide: a parameter for increased degradation of glycogen. Clin. Chim. Acta. 176: 39-48, 1988.

58. Kumlien, J., Grönberg, G., Nilsson, B., Månsson, O., Zopf, D.A., and Lundblad, A.: Structural and immunochemical analysis of three limit dextrin oligosaccharides. Arch. Biochem. Biophys. 269: 878-699, 1989.

59. Wang, W.T., and Zopf, D.A. Liquid ion-exchange chromatography of milk oligosaccharides using a pulsed amperometric detector. Carbohydr. Res. 189: 1-11, 1989.

60. Kumlien, J., Andren-Sandberg, A., Zopf, D., and Lundblad, A. Determination of a glucose-containing tetrasaccharide in urine of patients with acute pancreatitis. International Journal of Pancreatology. 4: 139-147, 1989.

61. Wang, W.T., Kumlien, J., Ohlson, S., Lundblad, A., and Zopf, D. Analysis of a glucose-containing tetrasaccharide by high-performance liquid affinity chromatography. Anal. Biochemistry. 182: 48-53, 1989.

62. Zopf, D.A., Ohlson, S., Dakour, J., Wang, W., and Lundblad, A. Analysis and Purification of Oligosaccharides by High-Performance Liquid Affinity Chromatography. In Ginsburg, V. (Ed.): Methods in Enzymology. New York, Academic Press, 1989, Vol. 179, pp. 55-64.

63. Zopf, D.A., and Ohlson, S. Weak-affinity chromatography. Nature. 346: No. 6279, 87-88, 1990.

64. Wang, W.T., Safar, J., and Zopf, D. Analysis of inositol by high-performance liquid chromatography. Anal. Biochemistry. 188: 432-435, 1990.

65. Wang, W.T., Erlansson, K., Lindh, F., Lundgren, T., and Zopf, D.A. High-performance liquid chromatography of sialic acid-containing oligosaccharides and acidic monosaccharides. Anal. Biochemistry. 190: 182-187, 1990.

66. Safar, J., Wang, W., Padgett, M.P., Ceroni, M., Piccardo, P., Zopf, D.A., and Gajdusek, D.C. Molecular mass, biochemical composition and physiochemical behavior of the infectious form of the scrapie precusor protein monomer. Proc. Natl. Acad. Sci. 87: 6373-6377, 1990.

67. Uppugundurl, S., Dakour, J., Kallin, E., Norberg, T., Zopf, D.A., and Lundblad, A. Affinity purification of monoclonal antibodies using a bifunctional oligosaccharide hapten. Glycoconjugate J. 8: 102-107, 1991.

68. Wang, W.T., Lundgren, T., Lindh, F., Nilsson, B., Grönberg, G., Brown, J.P., Mentzer-Dibert, H., and Zopf, D.A. Isolation of two novel sialyl-Lewis X-active oligosaccharides by high performance liquid chromatography using monoclonal Onc-M26. Arch. Biochem. Biophys. 292: 433-441, 1992.

69. Dakour, J., Zopf, D., and Lundblad, A.: Assay of alpha-1,3 N-Acetyl-D-Galactosaminyl Transferase by Affinity Chromatography. Anal. Biochemistry. 204: 210-214, 1992.

70. Ohlson, S. and Zopf, D. Weak affinity chromatography. in Kline, T., (ed) Handbook of Affinity Chromatography, Marcel Dekker, Inc., New York, 1993.

71. Ohlson, S., and Zopf, D. Weak affinity chromatography. In Ngo T.T. (ed) Molecular Interactions in Bioseparations, pp 15-25, Plenum Press, NY, 1993

72. Zopf, D.A. and Wang, W-T.: Purification of oligosaccharide antigens by weak affinity chromatography. In Garegg, P.J. (ed) Carbohydrate Antigens, ACS Symposium Series, American Chemical Society, Washington DC, 1993.

73. Roth, S. and Zopf, D.: Oligoaccharide pharmaceuticals. In Weiner, D.B. and Williams, W.V. (eds) Biological Approaches to Rational Drug Design. CRC Press, Ann Arbor, 1994.

74. Zopf, D. and Roth, S. Oligosaccharides as anti-infective drugs [Review]. Lancet, 347: 1017-1027 , 1996.

75. Zopf, D., Simon, P.M., Barthelson, R., Cundell, D., Idänpään-Heikkilä, I., Tuomanen, E.: Development of antiadhesion carbohydrate drugs for clinical use. In Kahane, I. and Ofek, I. (eds) Toward Anti-adhesion Therapy for Microbial Diseases, Plenum, NY pp. 35-38, 1996.

76. Simon, P.M., Goode, P.L., Mobasseri, A., and Zopf, D. Inhibition of *Helicobacter pylori* binding to gastrointestinal epithelial cells by sialic acid-containing oligosaccharides. Infect. Immun. 65: 750-757, 1997.

77. Idänpään-Heikkilä, I., Simon, P.M., Zopf, D., Vullo, T., Cahill, P., Sokol, K., and Tuomanen, E. Oligosaccharides interfere with the establishment and progression of experimental pneumococcal pneumonia. J. Infect. Diseases 176: 704-12, 1997.

78. Leickt, L., Bergström, M., Zopf, D., and Ohlson, S. Bioaffinity chromatography in the 10 mM range of Kd. Anal. Biochem. 253: 135-6, 1997.

79. Barthelson, R., Mobasseri, A., Zopf, D., and Simon, P. Adherence of *Streptococcus pneumoniae* to respiratory epithelial Cells is inhibited by sialylated oligosaccharides. Infect. Immun. 66: 1439-1444, 1998.

80. Simon, P.M., Neethling, F.A., Taniguchi, S., Goode, P.L., Zopf, D., Hancock, W.W., and Cooper, D.K.C. Intravenous infusion of Galα1-3Gal oligosaccharides in baboons delays hyperacute rejection of porcine xenografts. Transplantation 65: 346-53, 1998.

81. Ohlson, S., Bergstrom, M., Leickt, L., and Zopf, D. Weak affinity chromatography of small saccharides with immobilised wheat germ agglutinin and its application to monitoring of carbohydrate transferase activity. Bioseparation 7: 101-105, 1998

82. Fu, D., and Zopf, D. Analysis of sialyllactoses in blood and urine by high-performance liquid chromatography. Anal. Biochem. 269: 113-23, 1999.

83. Nakhla, T., Fu, D., Zopf, D., Brodshy, N.L., and Hurt, H. Neutral oligosaccharide content of preterm human milk. Brit. J. Nutr. 82: 361-7, 1999.

84. Mysore, G.V., Wigginton T., Simon, P.M., Zopf, D, Heman-Ackah L.M., and Dubois A. Treatment of *Helicobacter pylori* infection in rhesus monkeys using a novel antiadhesion compound. Gastroenterology 117: 1316-25, 1999

85. Simala-Grant, J. L., Zopf, D., and Taylor, D.E. Antibiotic susceptibility of attached and free-floating Helicobacter pylori. J. Antimicrob Chemo 47: 555-563, 2001

EXHIBIT E

ETH Eidgenössische Technische Hochschule Zürich

Ecole polytechnique fédérale de Zurich
Politecnico federale di Zurigo
Swiss Federal Institute of Technology Zurich

Professor Dr. James E. Bailey
Institute of Biotechnology

ETH Zürich
CH 8093 Zürich,
Switzerland

Tel.: 41-1-633 31 70
41-1-633 34 03
FAX: 41-1-633 10 51

Paul Simon, Ph.D.
V. P. for Research
VIMRx Pharmaceuticals, Inc.
2751 Centerville Rd., Suite 210
Wilmington, DE 19808
USA

FAX: +001 302 998-3794

Zurich, 22 February 1999

Dear Dr. Simon,

Thank you for your email message concerning antibody glycosylation. We do not anticipate any particular problems in implementing our glycosylation engineering strategy for improving antibody ADCC activity in large scale, high production cultures.

Of course, you are correct that glycosylation can be affected by process changes. In fact, we have prepared a comprehensive review of glycosylation, focusing more on genetic changes but also mentioning the process-related ones that have been reviewed recently elsewhere. I will send you a copy of this review by mail, since it is somewhat long. Unfortunately, it is available only in a book published as a conference preceding, so is not so widely accessible.

In general, I think that the process complications and costs associated with producing and utilizing a glycosyltransferase and also supplying the donor substrate make the exogenous manipulation of glycosylation generally far less attractive than engineering the cells to maximize the production of the desired glycoform. Also, you will see in the N-glycosylation pathway given in our paper that only one particular glycoform would be a suitable substrate for arriving at the desired final product, greatly reducing the potential yield of such exogenous glycosylation manipulation. Failure of much simpler cofactor-requiring enzyme catalyzed reactions to gain industrial success in competition with whole-cell biocatalysis speaks very strongly in my opinion against the competitive prospects *of in vitro* remodeling of glycosylation. I think it is much better to do this in the cells.

Best wishes,

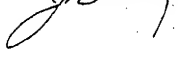


EXHIBIT F

Neose Signs R&D and Licensing Agreement with Wyeth-Ayerst

First Commercial Use of GlycoAdvance -- Novel Protein Glycosylation Technology

Horsham, PA, December 19, 2001 -- Neose Technologies, Inc. (NasdaqNM: NTEC) today announced that it has entered into a research, development and license agreement with Wyeth-Ayerst Laboratories, the pharmaceutical division of American Home Products Corporation (NYSE: AHP), for the use of Neose's GlycoAdvance™ technology to develop an improved production system for Wyeth's biopharmaceutical compound, rPSGL-Ig (P-selectin glycoprotein ligand). rPSGL-Ig is a P-selectin antagonist that is being developed to treat inflammation and thrombosis associated with acute coronary syndrome and reperfusion injury. It is currently being evaluated in Phase II clinical trials in patients being treated for heart attack. Wyeth is evaluating the use of GlycoAdvance in the production of rPSGL-Ig for Phase III clinical trials and commercial launch.

Neose will develop processes for the commercial-scale manufacture of proprietary enzymes and sugar nucleotides to be used in the production of rPSGL-Ig, and will license GlycoAdvance to Wyeth for commercial production of the drug. During commercial production of Wyeth's current rPSGL-Ig, Neose will receive ongoing payments tied to yield improvements achieved using GlycoAdvance in the production of rPSGL-Ig. In addition, Wyeth has the option to use GlycoAdvance to develop a next generation rPSGL-Ig, in which case Neose would receive royalties on product sales.

Under the agreement, Neose will receive license, research, and milestone payments that would total up to $17 million if all milestones are met. In addition to ongoing product payments, Neose and Wyeth will also enter into a supply agreement for the long-term supply of GlycoAdvance process reagents.

"We welcome Wyeth as our first commercial partner for GlycoAdvance and look forward to contributing to the success of rPSGL-Ig," says Stephen Roth, Ph.D., Neose's Chairman and CEO. "Wyeth and Neose have worked together extensively to show that GlycoAdvance can be applied to a drug in late stage clinical development. We are particularly excited to be working with Wyeth, given their significant investment in biopharmaceutical drug development, and their commitment to being a world leader in biologics manufacturing."

"GlycoAdvance gives us an important competitive advantage that complements our substantial and growing capital investment in manufacturing capacity," says L. Patrick Gage, Ph.D., President, Wyeth-Ayerst Research. "Using GlycoAdvance with rPSGL-Ig will help us launch the drug with manufacturing capacity in place to supply the projected needs of our initial indication, while giving us the flexibility to supply additional indications as they are developed."

Background on GlycoAdvance

There are more than 360 biotechnology drugs in development for more than 200 diseases. Many of these drugs are glycoproteins - proteins and antibodies that include complex carbohydrates, or sugar chains, as an integral part of their structure. In 2000, worldwide sales of protein and antibody drugs were about $20 billion. By 2010 worldwide sales are expected to exceed $90 billion. Many of these drugs will be glycoproteins and may be appropriate candidates for GlycoAdvance.

GlycoAdvance is Neose's proprietary enzymatic technology for completing the carbohydrate chains on glycoproteins after they have been produced in a biological expression system such as Chinese hamster ovary (CHO) cells. GlycoAdvance uses a class of enzymes, glycosyltransferases, to add individual sugar units onto the carbohydrate structures on glycoproteins. GlycoAdvance can be used with glycoprotein therapeutics, including fusion proteins and monoclonal antibodies, to extend half-life, increase effectiveness and improve manufacturing efficiency.

Glycoproteins contain complex carbohydrate structures attached to the protein portion of the molecule. These carbohydrates are integral to the structure and function of a glycoprotein and help determine how long the drug stays active in the body. Incomplete carbohydrate structures can result in the drug being cleared from the body too quickly, or may result in the drug being less effective. This means that a greater amount of the drug may be required to achieve the intended effect.

Achieving and maintaining the proper carbohydrate structures on glycoproteins is a major challenge in biotechnology manufacturing. Recombinant therapeutic glycoproteins are produced in living cells, usually CHO cells. The use of cell systems to produce glycoproteins requires balancing the cells' ability to produce protein with their ability to put on the required carbohydrates. As the cells' protein output increases, they do not maintain

the proper level of carbohydrates. This often results in low yields of usable product that adds to the cost and complexity of producing these drugs. These low yields are a significant contributor to the critical worldwide shortage of biologics manufacturing capacity.

Background on rPSGL-Ig

Wyeth's rPSGL-Ig is a recombinant version of the human PSGL-1 glycoprotein, linked to the Fc portion of a human antibody. PSGL-1 glycoprotein extends from the surface of white blood cells, or leukocytes, and helps the cells bind to the blood vessel wall in a process known as cell adhesion. PSGL-1 plays a critical role in the migration of these cells from the bloodstream to the site of tissue damage. This is an essential process in helping the body heal itself after an injury. However, in some instances, it can be harmful. Immediately following a heart attack, the leukocytes that attach to the damaged blood vessels exacerbate local inflammation that causes additional tissue damage.

rPSGL-Ig protects the site of tissue damage by preventing leukocytes and platelets from adhering and causing inappropriate inflammation and/or thrombosis. rPSGL-Ig is in Phase II clinical trials evaluating its ability to help accelerate clot dissolution and prevent reperfusion injury following a heart attack. rPSGL-Ig may also have use in solid organ transplantation and arterial vascular diseases including stroke.

About Neose Technologies

Neose develops proprietary technologies for the synthesis and manufacture of complex carbohydrates. The company uses its broad technology platform in the following programs: GlycoAdvance for correcting incomplete or incorrect glycosylation encountered in the manufacture of recombinant glycoproteins; GlycoTherapeutics to develop and produce novel carbohydrate-based therapeutics; and GlycoActives to develop and produce novel carbohydrate-based food ingredients.

Conference Call/Webcast

A conference call and webcast will be held for the investment community on Thursday, December 20, 2001, at 8:30 a.m. EST. The dial-in number for domestic callers is 800-967-7140. The dial-in number for international callers is 719-457-2629. A replay of the call will be available for 7 days beginning approximately four hours after the call's conclusion. The replay number for domestic callers is 888-203-1112 using the passcode 421599. The replay number for international callers is 719-457-0820, also using the passcode 421599. Live audio of the conference call will be simultaneously broadcast over the Internet through World Investor Link's Vcall website, located at www.vcall.com. To listen to the live call, please go to the web site at least fifteen minutes early to register, download, and install any necessary audio software. For those who cannot listen to the live broadcast, a replay will be available shortly after the call.

CONTACTS:

Neose Technologies, Inc.

Sr. Director, Corporate Communications

(215) 773-1802 Direct

(215) 441-5890 Main

(215) 285-1244 Cell

(610) 902-7336

Jason Rubin

(610) 941-2741

For more information, please visit www.neose.com.

"Safe Harbor" Statement under the Private Securities Litigation Reform Act of 1995: Statements in this press release that are not historical facts are "forward-looking statements" that involve risks and uncertainties. Among the risks are that the development of rPSGL-Ig using GlycoAdvance may not succeed, or rPSGL-Ig may not receive regulatory approval or be commercialized successfully. For a more detailed discussion of these risks and uncertainties, any of which could cause the Company's actual results to differ from those contained in any forward-looking statement, see the "Risk Factors" section of Item 1 of the Company's Annual Report on Form 10-K for the year ended December 31, 2000.

Neose Technologies, Inc.

EXHIBIT G

Neose Informed of Wyeth's Intention to Discontinue Development of rPSGL-Ig for Myocardial Infarction

Decision Unrelated to Neose's GlycoAdvance™

HORSHAM, PA, May 9, 2002 – Neose Technologies (NasdaqNM: NTEC) announced that it has been informed today by Wyeth Pharmaceuticals (NYSE: WYE) that Wyeth does not intend to continue clinical development of their compound, rPSGL-Ig, for myocardial infarction due to disappointing results in Phase II clinical trials. This decision was unrelated to the performance of Neose's GlycoAdvance technology. Although it is possible that development of rPSGL-Ig may continue for other indications, the timing or likelihood of continued development is not known.

Boyd Clarke, president and CEO of Neose Technologies, said, "We knew this compound was in Phase II clinical trials, and was subject to the normal risks and uncertainty associated with clinical drug development. Although our technology was working as planned, we are disappointed by the news from Wyeth. We hope to continue working with Wyeth to use GlycoAdvance in their therapeutic protein development programs."

Neose develops proprietary technologies for the synthesis and manufacture of complex carbohydrates. The company uses its broad technology platform in the following programs: GlycoAdvance products and services for correcting incomplete or incorrect glycosylation encountered in the manufacture of recombinant glycoproteins; GlycoTherapeutics™ to develop and produce novel carbohydrate-based therapeutics; and GlycoActives™ to develop novel carbohydrate-based food and nutritional ingredients.

CONTACTS:

Neose Technologies, Inc.

Matt Kremer

Sr. Director, Corporate Communications

A. Brian Davis

Acting Chief Financial Officer

(215) 315-9000

E-mail: info@neose.com

For more information, please visit www.neose.com.

"Safe Harbor" Statement under the Private Securities Litigation Reform Act of 1995: Statements in this press release that are not historical facts are "forward-looking statements" that involve risks and uncertainties. For a more detailed discussion of these risks and uncertainties, any of which could cause the Company's actual results to differ from those contained in any forward-looking statement, see the "Risk Factors" section of Item 1 of the Company's Annual Report on Form 10-K for the year ended December 31, 2001.

EXHIBIT H

Neose Technologies and MacroGenics Sign Research Collaboration and License Agreement

HORSHAM, Pa., and ROCKVILLE, Md., April 26 /PRNewswire-FirstCall/ -- Neose Technologies, Inc. (Nasdaq: NTEC) and MacroGenics Inc. announced today that the companies have entered into a research collaboration and license agreement on multiple monoclonal antibodies. Neose will apply its GlycoAdvance(TM) and GlycoPEGylation(TM) technologies to MacroGenics compounds with the goal of improving the therapeutic properties of these proteins.

MacroGenics has the right to take a limited number of remodeled compounds into development. Following the initial research phase, MacroGenics will be responsible for funding the further development of these licensed compounds under an exclusive license from Neose. In exchange, Neose will be entitled to receive various option fee, milestone, and royalty payments as products are developed and commercialized under the agreement.

"We are impressed with MacroGenics' expertise in the antibody field and look forward to working with them. They have important new technology for the development and modification of monoclonal antibodies, particularly in the Fc region, and we believe that combining our technologies may yield more effective new treatments for chronic diseases," said C. Boyd Clarke, Neose president, chief executive officer and chairman.

"We are excited by the potential therapeutic improvements that can be made to our monoclonal antibodies utilizing Neose's GlycoAdvance and GlycoPEGylation technologies," said Scott Koenig, M.D., Ph.D., president and chief executive officer of MacroGenics.

Neose is a biopharmaceutical company focused on the improvement of protein therapeutics through the application of its proprietary technologies. By applying its GlycoAdvance and GlycoPEGylation technologies, Neose is developing proprietary protein drugs that are improved versions of currently marketed therapeutics with proven efficacy. These second generation proteins are expected to offer significant advantages, such as less frequent dosing and improved safety and efficacy. In addition to developing its own products or co-developing products with others, Neose is entering into strategic partnerships for the inclusion of its technologies into products being developed by other biotechnology and pharmaceutical companies.

MacroGenics is a privately funded company focused on the development, manufacture and commercialization of biotechnology products including immunotherapeutics for cancer, infectious diseases, and autoimmune disorders. MacroGenics' core platform involves antibody receptor-related technologies which are employed to improve the ways cytotoxic antibodies mediate cell killing for the treatment of cancers and to prevent autoantibodies from triggering disease in autoimmunity.

CONTACTS:

Neose Technologies, Inc.
Robert I. Kriebel
Sr. Vice President and Chief Financial Officer

Barbara Krauter
Manager, Investor Relations
(215) 315-9000

For more information, please visit www.neose.com.

MacroGenics Inc.
Michael Richman
Exec. Vice President and Chief Operating Officer
(301) 251-5172

For more information, please visit www.macrogenics.com.

"Safe Harbor" Statement under the Private Securities Litigation Reform Act of 1995: Statements in this press release regarding our business that are not historical facts are "forward-looking statements" that involve risks and uncertainties. For a discussion of these risks and uncertainties, any of which could cause our actual results to differ from those contained in the forward-looking statement, see the section of Neose's Annual Report on Form 10-K for the year ended December 31, 2003, entitled "Factors Affecting the Company's Prospects" and

discussions of potential risks and uncertainties in Neose's subsequent filings with the SEC.

SOURCE Neose Technologies, Inc.

Neose Technologies, Inc. and Monsanto Protein Technologies Sign Research Agreement

HORSHAM, Pa., and ST. LOUIS, Nov. 25 /PRNewswire-FirstCall/ – Neose Technologies, Inc. (Nasdaq: NTEC) and Monsanto Protein Technologies, a unit of Monsanto Company (NYSE: MON), today announced that they have entered into a research agreement to investigate the use of Neose's GlycoAdvance(TM) technology to enhance the glycosylation of therapeutic monoclonal antibodies produced in plants.

Today, the majority of therapeutic monoclonal antibodies are produced by mammalian cell culture. The glycosylation patterns of plant-produced monoclonal antibodies differ significantly from monoclonal antibodies produced by mammalian cell culture. Monoclonal antibodies produced in plants have incomplete glycosylation patterns, resulting in the inability to activate the complement system and other types of critical effector function. This research will combine Monsanto Protein Technologies' expertise in transgenic plant production of monoclonal antibodies with Neose's expertise in glycosylation. This is expected to enhance the ability of plant-produced monoclonal antibodies to initiate complement activation.

"Monsanto believes this science promises tremendous benefits and will someday provide greater access to life-saving therapeutic drugs, thus providing more options for patients and doctors," said Cheryl Morley, President of Monsanto's Animal Ag and Protein Technologies Group. "We are excited about working with Neose and the GlycoAdvance technology."

"GlycoAdvance has the potential to make an important contribution to the glycosylation, and therefore the therapeutic usefulness of plant-produced proteins. We are delighted to be working with Monsanto, a leader in the development of plant-based systems," said C. Boyd Clarke, Neose president and chief executive officer.

Monsanto Protein Technologies, a unit of Monsanto, is focused on contract manufacturing of therapeutic proteins at very large scale derived from plant biotechnology. Monsanto is recognized as a leader in plant biotechnology and recombinant protein technology. By leveraging this breadth of experiences ranging from genomics and seed breeding, to large scale sterile protein manufacturing, Monsanto Protein Technologies can deliver a cost-effective process for producing therapeutic proteins at very large scale.

Neose develops proprietary technologies for using enzymes to manufacture complex carbohydrates. Neose is using its broad technology base to develop novel and improved products for itself and its partners, primarily focusing on protein therapeutics. Neose markets its technology for improving protein drugs under the name GlycoAdvance. GlycoAdvance is used to modify the human carbohydrate structures on therapeutic glycoproteins. Neose is also developing its technology to create novel glycosylation patterns, and to link other molecules, such as polyethylene glycol, to glycoproteins. The application of this technology to proteins potentially results in improved clinical activity and pharmacokinetic profile, enhanced drug development flexibility, stronger and additional patent claims, and yield improvements.

For more information pertaining to Neose Technologies, Inc., please visit http://www.neose.com.

For more information pertaining to Monsanto Protein Technologies, please visit http://www.mpt.monsanto.com.

Cautionary Statements Regarding Forward-Looking Information of

Neose Technologies, Inc.:

Statements in this press release regarding our business that are not historical facts are "forward-looking statements" that involve risks and uncertainties. For a discussion of these risks and uncertainties, any of which could cause our actual results to differ from those contained in the forward-looking statement, see the "Risk Factor" section of Item 1 of our Annual Report on Form 10-K for the year ended December 31, 2001.
Cautionary Statements Regarding Forward-Looking Information of Monsanto Company and Monsanto Protein Technologies (a unit of Monsanto Company):

Certain statements contained in this release, such as statements concerning the anticipated financial results, current and future product performance, regulatory approvals, currency impact, business and financial plans and other non-historical facts pertaining to Monsanto Company or Monsanto Protein Technologies, Inc. are "forward-looking statements." These statements are based on current expectations and currently available information. However, since these statements are based on factors that involve risks and uncertainties, the actual performance and results of Monsanto Company or Monsanto Protein Technologies, Inc. may differ materially from those described or implied by such forward-looking statements. Factors that could cause or contribute to such

differences include, among others: the success of the research and development activities of Monsanto Company and Monsanto Protein Technologies, Inc. and the speed with which regulatory authorizations and product launches may be achieved; the ability of Monsanto Company or Monsanto Protein Technologies, Inc. to successfully market new and existing products in new and existing domestic and international markets; the ability of Monsanto Company or Monsanto Protein Technologies, Inc. to achieve and maintain protection for its respective intellectual property; the exposure of Monsanto Company or Monsanto Protein Technologies, Inc. to lawsuits and other liabilities and contingencies, including those related to intellectual property, product liability, regulatory compliance, environmental contamination and antitrust; and other risks and factors detailed in the Monsanto Company's filings with the U.S. Securities and Exchange Commission. Undue reliance should not be placed on these forward-looking statements, which are current only as of the date of this release. Monsanto Company and Monsanto Protein Technologies, Inc. disclaim any current intention to revise or update any forward-looking statements or any of the factors that may affect actual results, whether as a result of new information, future events or otherwise.

CONTACTS:

Neose Technologies, Inc.
Robert I. Kriebal
Sr. Vice President and
Chief Financial Officer
215-315-9000

Barbara Krauter
Investor Relations Associate
215-315-9000

Monsanto Protein Technologies
Lee Quarles
Monsanto Public Affairs
314-694-4452

Jon McIntyre, Ph.D.
Chief Scientist
314-694-8428

SOURCE Neose Technologies, Inc.

Neose and Novo Nordisk Sign Research and Development Collaboration Agreement

HORSHAM, Pa., Oct. 1 /PRNewswire-FirstCall/ –
Neose Technologies, Inc. (Nasdaq: NTEC) today announced that it has entered into a research and development collaboration agreement with Novo Nordisk A/S (NYSE: NVO) for the use of Neose's GlycoAdvance™ technology to make clinically significant improvements to a Novo Nordisk therapeutic protein.

We believe Neose's GlycoAdvance technology may make important improvements to marketed therapeutic proteins in the Novo Nordisk pipeline. As a global leader in the development and commercialization of biological products, Novo Nordisk is an ideal partner for GlycoAdvance. We are excited by the potential opportunities to add value to their products through this collaboration, said C. Boyd Clarke, Neose president and chief executive officer.

Novo Nordisk is a focused healthcare company and the world leader in diabetes care. In addition, Novo Nordisk has a leading position within areas such as haemostasis management, growth hormone therapy and hormone replacement therapy. Novo Nordisk manufactures and markets pharmaceutical products and services that make a significant difference to patients, the medical profession and society. With headquarters in Denmark, Novo Nordisk employs approximately 17,900 people in 68 countries and markets its products in 179 countries. For further company information visit www.novonordisk.com.

Neose develops proprietary technologies for using enzymes to manufacture complex carbohydrates. Neose is using its broad technology base to develop novel and improved products for itself and its partners, primarily focusing on protein therapeutics. Neose markets its technology for improving protein drugs under the name GlycoAdvance™. We use GlycoAdvance™ to modify the human carbohydrate structures on therapeutic glycoproteins. We are also developing our technology to create novel glycosylation patterns, and to link other molecules, such as polyethylene glycol, to glycoproteins. The application of this technology to proteins potentially results in improved clinical activity and pharmacokinetic profile, enhanced drug development flexibility, stronger and additional patent claims, and yield improvements. We are exploring the use of our technology to enable the development of carbohydrate-based therapeutics, and the development of novel carbohydrate food and nutritional ingredients.

CONTACTS:

Neose Technologies, Inc.

Robert I. Kriebel

Sr. Vice President and Chief Financial Officer

Barbara Krauter

Investor Relations Associate

(215) 315-9000

For more information, please visit www.neose.com.

Safe Harbor Statement under the Private Securities Litigation Reform Act of 1995: Statements in this press release regarding our business that are not historical facts are forward-looking statements that involve risks and uncertainties. For a discussion of these risks and uncertainties, any of which could cause our actual results to differ from those contained in the forward-looking statement, see the Risk Factor section of Item 1 of our Annual Report on Form 10-K for the year ended December 31, 2001.

SOURCE Neose Technologies, Inc.

/CONTACT: Robert I. Kriebel, Sr. Vice President and Chief Financial Officer, or Barbara Krauter, Investor Relations Associate, both of Neose Technologies, +1-215-315-9000/

/Web site: http://www.novonordisk.com /

/Web site: http://www.neose.com /

(NTEC NVO)

CO: Neose Technologies, Inc.; Novo Nordisk A/S
ST: Pennsylvania, Denmark
IN: MTC BIO HEA
SU: JVN CON

FB
-- PHTU058 --
4515 10/01/2002 16:01 EDT http://www.prnewswire.com

EXHIBIT IV